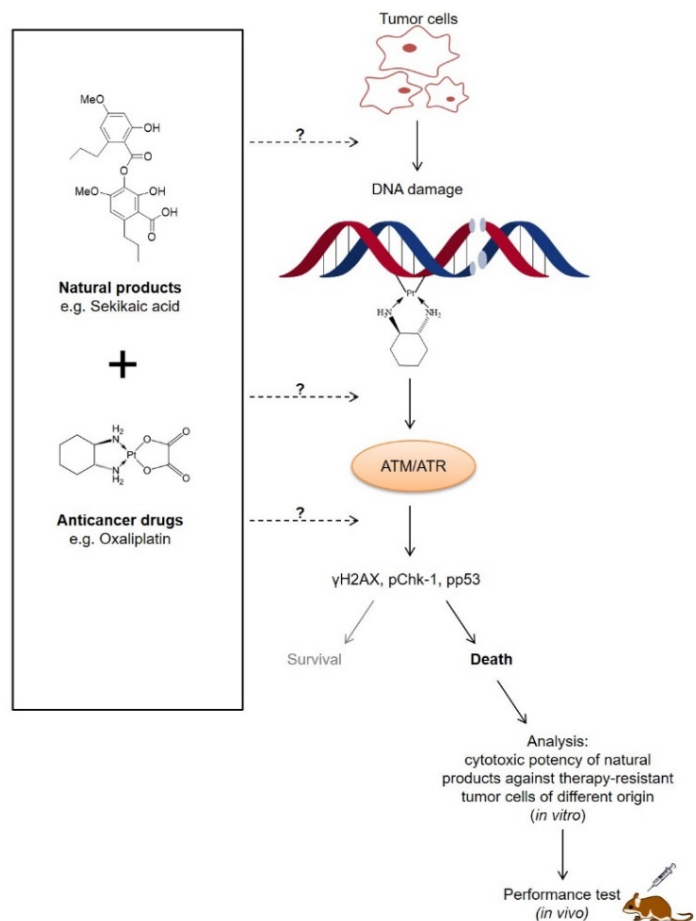


Targeting mechanisms of DNA damage response (DDR) to overcome anticancer drug resistance of tumor cells



The therapeutic efficacy of conventional anticancer therapeutics (cAT) is the genomic DNA of tumor cells. In consequence of DNA damage induction, a complex stress response program, named DNA damage response (DDR), gets activated. The PI3-like protein kinases ATM and ATR are key regulators of the DDR because they ensure the coordinated regulation DNA repair, activation of cell cycle checkpoints and apoptosis. The aim of the study is to identify natural compounds that interfere with the DDR, thereby re-sensitizing resistant tumor cells to cAT. Pancreatic carcinoma cells harbouring mutated p53 and oncogenic Ki-Ras will be initially employed as *in vitro* model. Following the screening of a natural compound library, specific substances will be identified that influence the DDR of malignant cells stimulated by selected cAT (e.g. oxaliplatin). As a read-out of the DDR activation status, ATM/ATR-catalyzed phosphorylation of histone H2AX, checkpoint kinases and p53 will be monitored. DDR modifying natural compounds that have been identified will further be characterized regarding their impact on the survival and viability of cAT-treated tumor cells of different origin (*in vitro* and *in vivo* studies).

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